REVIEW

Egg Consumption and Risk of All-Cause and Cause-Specific Mortality: A Systematic Review and Dose-Response Meta-analysis of Prospective Studies

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ABSTRACT

The association between egg consumption and mortality is extremely debatable. This study aimed to investigate the potential dose-response association of egg consumption with risk of mortality from all causes and cause-specific in the general population. The primary comprehensive literature search was conducted in PubMed/Medline, Scopus, ISI Web of Science, and Embase up to March 2021, as well as reference lists of relevant original papers and key journals. We calculated summary RRs and their 95% CIs for the highest and lowest categories, as well as the linear trend estimation of egg intake, using the random-effects model. Thirty-three (32 publications) cohort studies were included. These studies enrolled 2,216,720 participants and recorded 232,408 deaths from all causes. Comparing highest versus lowest egg intake categories was not associated with the risk of mortality from all causes (RR: 1.02; 95% CI: 0.94, 1.11; $n = 25$), cardiovascular disease (CVD) (RR: 1.04; 95% CI: 0.87, 1.23, $n = 11$), coronary heart disease (CHD) (RR: 0.98; 95% CI: 0.84, 1.16; $n = 10$), stroke (RR: 0.81; 95% CI: 0.64, 1.02; $n = 9$), and respiratory disease (RR: 0.96; 95% CI: 0.53, 1.71; $n = 3$); however, it was associated with a higher risk of cancer mortality (RR: 1.20; 95% CI: 1.04, 1.39; $n = 13$). In the linear dose-response analysis, an additional intake of 1 egg per week was associated with a 2% and 4% increased risk of all-cause and cancer mortality, respectively, and a 4% decreased risk of stroke mortality. The certainty of the evidence was rated as low to moderate. Higher egg consumption was not associated with an increased risk of mortality from all causes, CVD, CHD, stroke, or respiratory disease, whereas an elevated risk was observed for cancer mortality. These findings suggest that eggs be consumed in low to moderate amounts ($\leq$1 egg/d) as part of a healthy diet. *Adv Nutr* 2022;13:1762–1773.

Statement of Significance: Higher egg consumption was not associated with risk of mortality from all causes, CVD, CHD, stroke, and respiratory disease. Higher egg consumption was associated with an increased risk of cancer mortality. Each additional egg per week consumption was associated with a 2% and 4% increased risk of all-cause and cancer mortality.

Keywords: egg, mortality, cardiovascular disease, stroke, cancer, all-cause mortality

Introduction

Noncommunicable diseases, which include cardiovascular disease (CVD), stroke, cancer, and chronic respiratory disease, are the leading causes of death and disability in the world, accounting for 70% of all deaths (1). Assessment of contributing factors, including dietary factors, to all-cause and cause-specific mortality is a research priority worldwide (2). The association between high serum concentrations of LDL cholesterol and all-cause and cause-specific mortality, namely coronary heart disease (CHD) and stroke, is well documented (3, 4). The influence of dietary cholesterol on serum cholesterol and its role in all-cause and cause-specific

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mortality has been widely debated. Although dietary cholesterol was previously thought to influence serum cholesterol concentrations, the last guideline of the American Heart Association did not set any restrictions on dietary cholesterol intake (5, 6). Nevertheless, consuming lower amounts of dietary cholesterol is generally recommended as part of a healthy, balanced diet (6, 7). Eggs, in particular egg yolks, are a notable source of dietary cholesterol, and contain approximately 200 mg cholesterol (6, 8). In addition to cholesterol, egg is an affordable source of several nutrients, including B vitamins, choline, folate, minerals, MUFAs, and proteins (9). Egg consumption has regained popularity in recent years worldwide as they are recommended as a healthy component of diets (10). In particular, consumption in the European Union averages 240 eggs per person per year, and a similar overall increase in global consumption has been seen, highlighting the importance of thoroughly understanding any adverse effects of egg consumption (11).

Egg consumption in moderation is still recommended in dietary guidelines; however, recommended consumption differs considerably depending on the guideline and country, highlighting the lack of clarity surrounding egg consumption and the benefits and adverse effects on health (6, 12, 13). Egg consumption has been investigated in relation to several health-related outcomes, albeit with conflicting results. Djoussé et al. (12) found no significant association between egg consumption and risk of myocardial infarction and stroke; however, the authors reported a positive association with mortality, particularly in diabetic patients. Similarly, a large Italian cohort reported an increased risk of all-cause, CVD, and cancer mortality with eating over 4 eggs/wk (14). In a meta-analysis of 8 prospective studies in 2017, Schwingshackl et al. (15) reported that intake of 60 g egg/d was associated with a 10% increased risk of all-cause mortality. However, several large-scale cohort studies were not included in that analysis (16–18). In addition, they did not consider cause-specific deaths. In addition, more than 10 prospective cohort studies were published after the appearance of that meta-analysis and findings from these studies were not in line with the results of that meta-analysis (10, 19–24). For instance, Dehghan et al. (25) found no significant associations between egg consumption and risk of mortality in a study across 50 different countries. Therefore, we conducted this study to update an earlier meta-analysis by systematically reviewing published studies on egg consumption and the risk of all-cause and cause-specific mortality, as well as a dose-response meta-analysis to summarize the reported effect sizes in the published studies.

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Abbreviations used: CHD, coronary heart disease; CVD, cardiovascular disease; ROBINS-I, Risk of Bias in Non-randomized Studies of Intervention.

Methods

This systematic review and meta-analysis was reported in compliance with the standards of the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guideline (26). The protocol of this study was a priori registered and is accessible at International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/PROSPERO, ID = CRD42021242666).

Search strategy

Literature searches were undertaken at PubMed/Medline, Scopus, ISI Web of Science, and Embase from inception up to March 2021. The search specialist applied no language or date restrictions. We used relevant search terms for the study exposure (egg) AND outcomes (mortality) AND study design (prospective studies). Detailed information on the search strategy for each electronic database is provided in **Supplemental Table 1**. We also reviewed the reference lists of all relevant original articles and reviews as sources of more qualified studies. In addition, key journals were hand-searched.

Study selection

The abstract and full-text screening was performed by 2 independent authors (SMM and NZ), and relevant studies were included based on the following eligibility criteria: *1*) prospective cohort studies that were conducted in adults in the general population; *2*) studies that reported egg consumption as the exposure; *3*) studies that considered the incidence of mortality from all-cause and/or other causes, including coronary CHD, CVD, stroke, cancer, and respiratory diseases, as an outcome of interest; and *4*) reported adjusted effect estimates as RRs or HRs with corresponding 95% CIs. Any conflicts were solved through discussion or by involving a third reviewer (AE).

We selected studies that provided the following data to perform dose-response analyses: a quantitative measure of egg consumption (i.e., servings/day or week, numbers/day or week, grams/day or week) for 2 or more categories with the corresponding adjusted RRs and 95% CI, category-specific, or the total numbers of cases and noncases or person-years. Studies that reported continuous estimation from the associations were included as well. For studies that reported data from the same cohort, the one with complete data or a higher number of cases was included in our meta-analysis. The list of excluded studies and the relevant reasons are provided in **Supplemental Table 2**.

Data extraction

Data extraction was performed by 2 study authors in duplicate (SMM and NZ), and the following information was extracted: first author's last name, study name, publication year, study location, follow-up period, range or mean age at entry, sex, total sample size and the number of deaths, dietary assessment method, outcome assessment method, egg consumption frequency or amount or unit of egg intake, and the fully adjusted risk estimates with corresponding

95% CIs and the list of potential confounders. When the studies had adjusted for intermediate variables, including hypertension, diabetes, blood pressure, or lipid profile in their fully adjusted model, effect sizes from a model without controlling for these intermediate variables were considered in the analysis, if available. If a study had reported gender-specific risk estimates, we combined them by the fixed-effects model to include each cohort once in the main analysis.

Assessment of risk of bias and certainty of evidence

The Risk of Bias in Non-Randomized Studies of Intervention (ROBINS-I) tool was used to assess the risk of bias (27). It includes the risk of bias due to confounding factors, the selection of study participants, the classification of interventions, deviations from the intended intervention, missing data, outcome measurement, and the selection of the reported results. Each study was evaluated independently by 2 investigators (SMM and ABP), who addressed any disagreements by mutual conversation or the consultation of a third reviewer (AE). The risk-of-bias judgments for each domain are depicted in **Supplemental Figure 1**.

The updated Grading of Recommendations Assessment, Development, and Evaluations (GRADE) system, which incorporates the application of ROBINS-I, was used to assess the certainty of evidence for each association (28).

Data synthesis and statistical analysis

We considered the RRs and their 95% CIs as the effect size for the present study. HRs in the initial studies were assumed equal to RR (29). The summary RRs of all-cause and cause-specific mortality were calculated for the highest compared with the lowest category of egg consumption and for the 1-egg/wk increment using the DerSimonian–Laird random-effects model (30), which considers both within- and between-study variation (heterogeneity). For studies that reported continuous estimation for the associations, we converted the RRs per-unit increment risk estimates to the highest versus the lowest level of intake by using the average difference between the midpoints of the upper and lower categories in other included studies in the analysis (31).

We performed linear dose-response analysis by the method introduced by Greenland and Longnecker (32) and Orsini (33). We calculated the RRs and 95% CIs for a 1-egg/wk increment in egg consumption for each study. For this purpose, the distribution of cases and person-years and median or range of egg consumption with corresponding effect estimates across categories must be reported. The median of egg consumption in each category was considered. When egg intake was reported as a range, we estimated each category's midpoint by calculating the average of the lower and upper bounds. Median egg consumption in each category was allocated to the corresponding RR. When the highest and lowest categories were open-ended, we assumed the length of these categories to be the same as that of the adjacent intervals. For studies that reported egg intake as servings or grams/day or per week, we converted them to the number of eggs/week by assuming the weight of each egg as 50 g and the portion size of 1 serving as 1 egg. The potential nonlinear association was modeled using restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the distribution (34). The correlation within each category of RRs was considered and the study-specific estimates were combined using a 1-stage linear mixed-effects meta-analysis (35). This approach estimates the study-specific slope lines and combines them to obtain an overall average slope in a single stage and is a more accurate, flexible, and efficient approach compared with the traditional 2-stage method (32, 36).

We used Cochran's Q test (37) and I^2 statistic (38) to estimate the proportion of total variability due to between-study heterogeneity. We also used subgroup and meta-regression analyses to find potential sources of heterogeneity by geographical location (United States, Europe, Asia), gender (men, women, both), follow-up period ($<$15 y, $\geq$15 y), dietary assessment method (food-frequency questionnaire/food record), mean egg intake ($<$3/wk, $\geq$3/wk), number of deaths, adjustment for key covariates (energy intake, smoking, BMI, physical activity, and alcohol intake), and intermediates (hypertension, diabetes, blood pressure, serum cholesterol). We performed influence analysis by omitting each cohort one at a time to investigate the robustness of the pooled effect sizes. When 10 or more studies were available, publication bias was assessed using visual inspection of the funnel plot and Egger's regression test (39). For statistical analyses, Stata software, version 15.0 (StataCorp), was used. *P* values of less than 0.05 were regarded as significant.

Results

The initial database search yielded 10,987 results. After removing 3821 duplicate records and 7077 records based on title and abstract, 90 potentially relevant publications were considered for further review. Following a full-text review, we included 33 cohort studies (32 publications) in the analyses (10, 12, 16–25, 40–59) (Supplemental Table 2). Twenty-five cohorts (24 publications) were included in the analysis of all-cause mortality, 11 studies in the analysis of CVD mortality, 10 studies in the analysis of CHD mortality, and 9, 13, and 3 studies in the analysis of stroke mortality, cancer mortality, and respiratory disease mortality, respectively. Results of the literature search, screening, and selection process are displayed in **Figure 1**.

Of these studies, 9 were from the United States (12, 16, 19, 40, 46, 47, 48, 57, 59), 9 from Europe (10, 22, 23, 41, 49, 50, 52, 55, 58), 12 from Asia (17, 18, 20, 21, 24, 42–45, 51, 53, 54), and 1 study was a multinational study conducted among 21 countries (25). These studies enrolled a total of 2,216,720 participants, ranging from 960 to 521,120. During a 6- to 32-y period of follow-up, 232,408 deaths from all causes, 65,771 from CVDs, 6710 from CHD, 7728 from stroke, 60,799 from cancer, and 2161 from respiratory disease were documented. These studies were published between 1984 (16) and 2021 (58, 59). Mean age across studies differed from 33.5 (41) to 63 (57) y. Seven studies included only men (12,

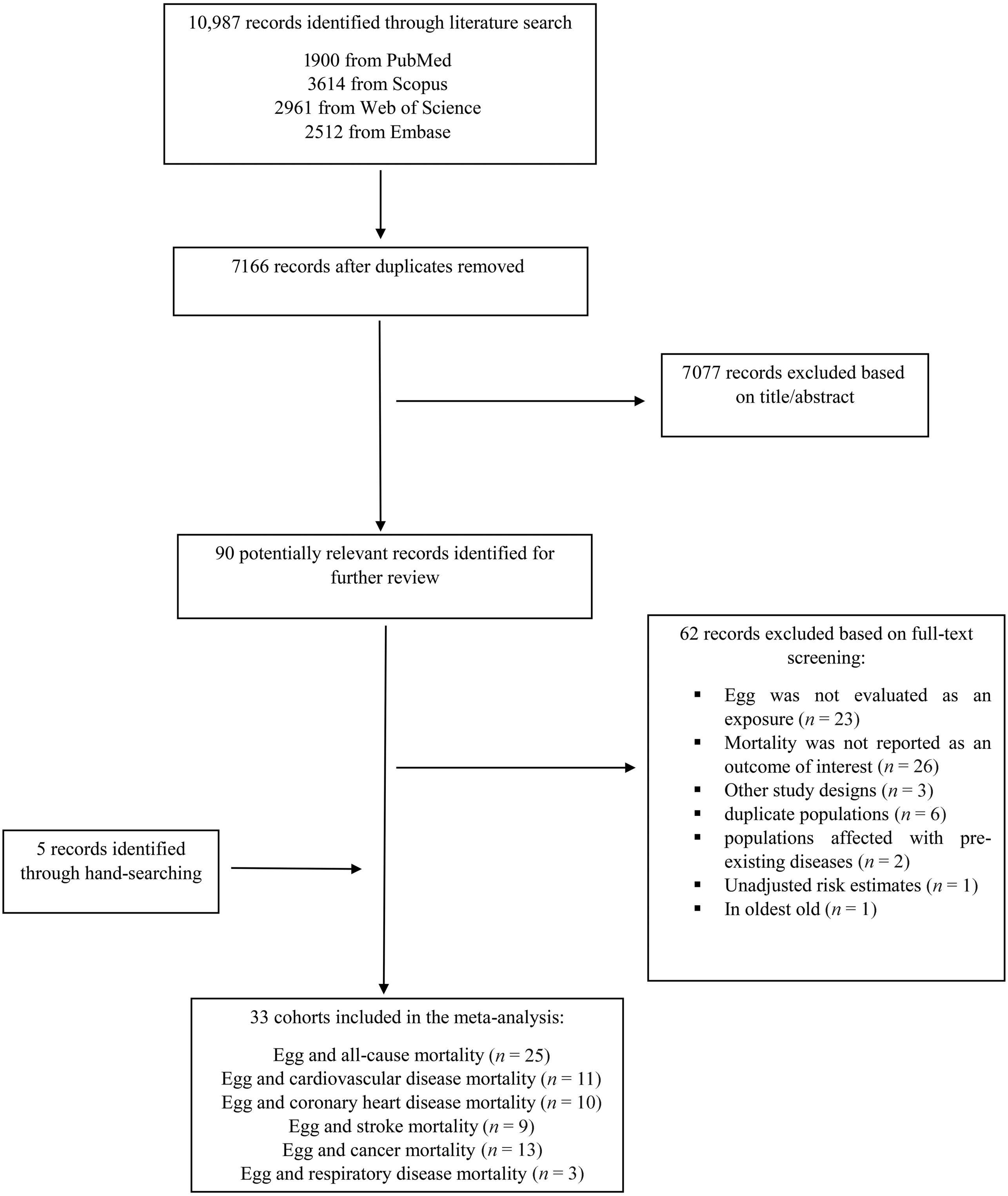

FIGURE 1 Flow diagram of screening and selection process of the included studies.

17, 23, 40, 47, 50, 52), 3 cohorts included only women (17, 53, 57), and others included either gender. Main characteristics of included studies are presented in **Supplemental Tables 3–8**, separately for each outcome.

Egg and all-cause mortality

Twenty-five cohort studies (24 publications) (12, 16–25, 41, 45, 46, 49–53, 55–59) investigated the association between egg consumption and risk of all-cause mortality, including

1,541,769 participants and 232,408 deaths. Comparing the highest with the lowest category of egg consumption, the pooled RR from the random-effects model indicated no significant association between egg consumption and risk of all-cause mortality (RR: 1.02; 95% CI: 0.94, 1.11), with a considerable heterogeneity between studies ($I^2 = 95.4\%$, *P*-heterogeneity < 0.001) (**Supplemental Figure 2**, **Table 1**). In the sensitivity analysis, we found that this association did not depend on an individual study, suggesting that exclusion of each study at a time did not change the pooled results (**Supplemental Figure 3**). Further analysis was done by considering the effect sizes derived from models that had adjusted for potential intermediate risk factors (including lipid profiles). Findings from these analyses revealed the same results (RR: 1.03; 95% CI: 0.97, 1.10; $I^2 = 89.6\%$; **Supplemental Figure 4**). The summary RR for men was 1.01 (0.82, 1.24; $n = 6$) and 1.09 (0.85, 1.38; $n = 4$) for women.

Twenty-one studies provided adequate information for inclusion in the dose-response meta-analysis (12, 17–22, 24, 25, 41, 45, 46, 49, 51–53, 55–59). According to the linear meta-analysis, an additional intake of 1 egg/wk was associated with a 2% increased risk of all-cause mortality (RR: 1.02; 95% CI: 1.00, 1.03; **Supplemental Figure 5**). However, there was no evidence of a nonlinear association between egg intake and risk of all-cause mortality (*P*-nonlinearity = 0.20; **Figure 2**) and **Supplemental Table 9**).

When we stratified the studies by geographic location in the subgroup analysis, an 18% higher risk of all-cause mortality was observed across studies conducted in the United States (RR: 1.18; 95% CI: 1.10, 1.26; $n = 7$). A similar association was observed in populations that consumed less than 3 eggs/wk (RR: 1.14; 95% CI: 1.04, 1.25; $n = 14$) and among studies with a higher number of deaths (>5000 deaths) (RR: 1.15; 95% CI: 1.04, 1.28; $n = 9$) (**Supplemental Table 10**). Surprisingly, an inverse association was observed in studies conducted in Asia (RR: 0.89; 95% CI: 0.80, 0.99; $n = 9$) and in populations that consumed more than 3 eggs/wk (RR: 0.88; 95% CI: 0.80, 0.98; $n = 11$). There was also evidence of publication bias based on visual inspection of the funnel plot (**Supplemental Figure 6**A), which was confirmed by Egger's test ($P = 0.01$). The evidence was graded as low quality, with downgrades for inconsistency, indirectness, and publication bias, but an upgrade for dose-response gradients (**Supplemental Table 11**).

Egg consumption and CVD mortality

Eleven prospective cohorts (10, 18, 24, 25, 53–59), including 1,403,111 participants and 65,771 CVD deaths, were included in the highest versus lowest category of egg intake. The summary RR based on the random-effects model was 1.04 (95% CI: 0.87, 1.23), with a considerable evidence of heterogeneity ($I^2 = 95.0\%$, *P*-heterogeneity < 0.001) (**Supplemental Figure 7**, Table 1). The association remained unchanged when adjusted effect sizes for intermediate confounding variables were considered (RR: 1.05; 95% CI: 0.94, 1.18; $I^2 = 87.3\%$; **Supplemental Figure 8**). However,

TABLE 1 Egg consumption in relation to risk of all-cause and cause-specific mortality based on analysis of the highest compared with lowest intake, as well as a dose-response analysis

	Highest vs. lowest analysis						Dose-response analysis					
	Sample size, *n*	Deaths, *n*	Studies, *n*	RR (95% CI)	I^2, %	*P*-heterogeneity	Dose, eggs/wk	Studies, *n*	RR (95%CI)	I^2, %	*P*-heterogeneity	Quality of evidence
Mortality												
All-cause	1,541,769	232,408	25	1.02 (0.94, 1.11)	95.4	<0.001	1	22	1.02 (1.00, 1.03)	97.7	<0.001	Low
Cardiovascular disease	1,403,111	65,771	11	1.04 (0.87, 1.23)	95.0	<0.001	1	10	1.00 (0.97, 1.04)	96.6	<0.001	Moderate
Coronary heart disease	667,400	6710	10	0.98 (0.84, 1.11)	72.0	<0.001	1	10	1.00 (0.96, 1.03)	71.6	<0.001	Moderate
Stroke	676,385	7728	9	0.81 (0.64, 1.02)	88.2	<0.001	1	9	0.96 (0.92, 0.99)	86.7	<0.001	Moderate
Cancer	895,308	60,799	13	1.20 (1.04, 1.39)	93.6	<0.001	1	12	1.04 (1.01, 1.07)	91.2	<0.001	Moderate
Respiratory disease	149,474	2161	3	0.96 (0.53, 1.72)	88.4	<0.001	1	3	0.99 (0.91, 1.08)	78.9	<0.001	Moderate

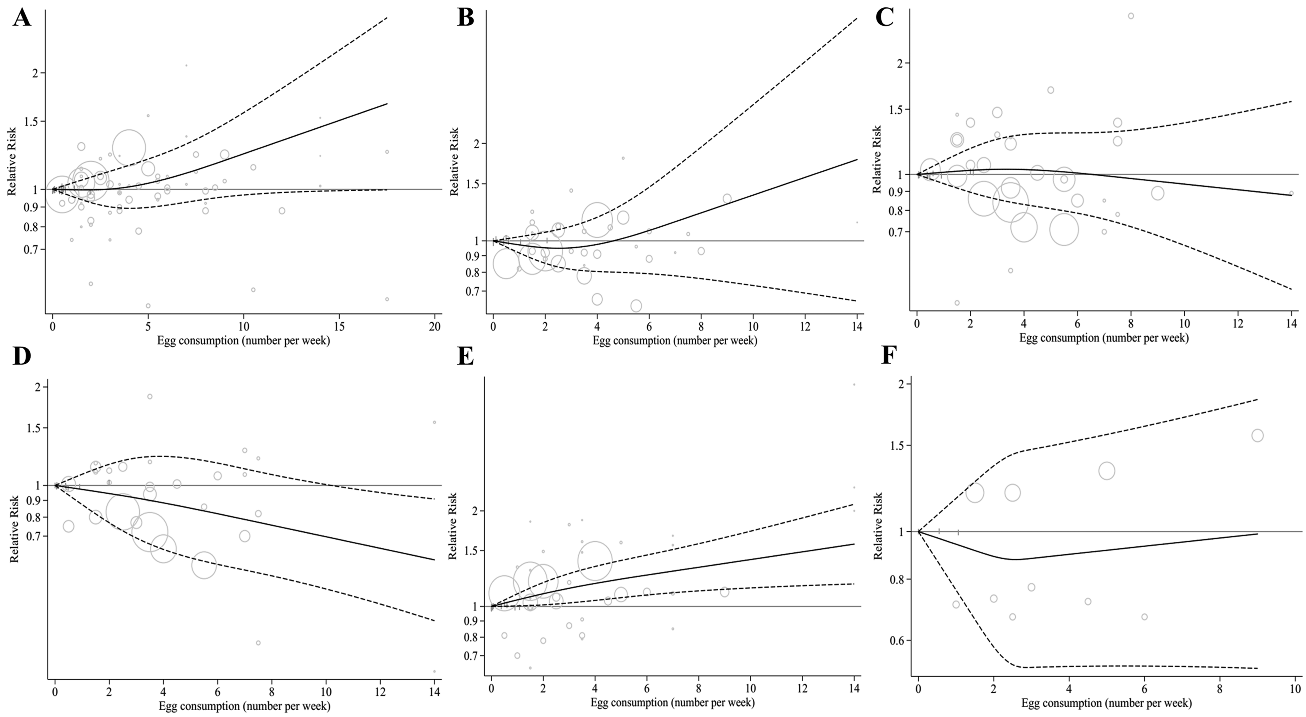

FIGURE 2 Nonlinear dose-response association between egg consumption and risk of mortality from all causes (A), cardiovascular diseases (B), coronary heart disease (C), stroke (D), cancer (E), and respiratory disease (F). The solid lines represent nonlinear dose-response, and dotted lines represent 95% CIs. Circles represent RR point estimates for egg consumption categories from each study, with the circle size proportional to the inverse of standard error.

this association was influenced by the results of the China Kadoorie Biobank (CKB) study; excluding that study from the analysis resulted in a significant positive association (RR: 1.09; 95% CI: 1.01, 1.19; **Supplemental Figure 9**).

All studies, except for 1 (56), reported sufficient data for inclusion in the dose-response analysis. An additional intake of 1 egg/wk was not associated with an elevated risk of CVD mortality (RR: 1.00; 95% CI: 0.97, 1.04; **Supplemental Figure 10**). In the nonlinear analysis, we found a J-shaped relation between egg consumption and CVD mortality, such that consumption of up to 3 eggs/wk was associated with a decreased risk; however, this association was not significant (P-nonlinearity = 0.11, Figure 2 and Supplemental Table 9).

Based on the subgroup analyses, gender, duration of follow-up, number of cases, and adjustment for BMI, hypertension, and diabetes were the potential sources of heterogeneity (**Supplemental Table 12**). There was a significant association in studies conducted in the United States (RR: 1.20; 95% CI: 1.10, 1.31; $n = 3$), populations that consumed less than 3 eggs/wk (RR: 1.12; 95% CI: 1.02, 1.24; $n = 7$), studies that included both genders (RR: 1.35; 95% CI: 1.20, 1.51; $n = 9$), and those with 15 y or more duration of follow-up (RR: 1.18; 95% CI: 1.10, 1.27; $n = 5$). There was no evidence of publication bias ($P = 0.49$) (Supplemental Figure 6B). The certainty in the estimates was rated as moderate, with downgrades for inconsistency and indirectness, and an upgrade for dose-response gradients (Supplemental Table 11).

Egg and CHD mortality

Ten prospective cohorts (10, 18, 19, 24, 41, 45, 48, 51, 54, 58) evaluated the relation of egg intake with risk of mortality from CHD, including 667,400 participants and 6710 events. Pooling effect sizes revealed that egg consumption was not associated with risk of CHD mortality (RR: 0.98; 95% CI: 0.84, 1.16), with a substantial heterogeneity across studies ($I^2 = 72.2\%$, P-heterogeneity < 0.001) (**Supplemental Figure 11**, Table 1). By removing each primary study one at a time and restarting the analysis, this association did not reach statistical significance (**Supplemental Figure 12**). When the adjusted effect sizes for intermediate variables were considered in the analysis, the association did not change (RR: 0.98; 95% CI: 0.88, 1.08; $I^2 = 35.3\%$; **Supplemental Figure 13**). All studies were included in the dose-response analysis. The summary RR for CHD mortality with an increment of 1 egg intake/wk was 1.00 (95% CI: 0.96, 1.03; **Supplemental Figure 14**). We also did not find a curve relation in the nonlinear dose-response evaluation (P-nonlinearity = 0.57; Figure 2 and Supplemental Table 9).

Findings from the subgroup analyses suggested that geographical location, duration of follow-up, and adjustment for energy intake, smoking, BMI, physical activity, hypertension, blood pressure, serum cholesterol, and diabetes were potential sources of heterogeneity (**Supplemental Table 13**). The summary RR for men was 1.31 (0.82, 2.10; $n = 2$) and 0.82 (0.37, 1.85; $n = 2$) for women. In addition, there was no significant association across subgroups, except for studies with more than 500 deaths from CHD (RR: 0.81; 95% CI: 0.67, 0.98; $n = 3$). The visual inspection of the funnel plot (Supplemental Figure 6C) and Egger's regression test ($P = 0.49$) did not provide evidence of publication bias. The certainty of evidence was graded as moderate (Supplemental Table 11).

Egg and stroke mortality

The association of the highest compared with the lowest categories of egg consumption and stroke mortality was investigated in 9 prospective studies (10, 18, 19, 24, 42, 45, 48, 51, 54) based on 676,385 subjects, including 7728 deaths. When the effect sizes from these studies were combined, they revealed no significant inverse relation between egg consumption and stroke mortality risk (RR: 0.81; 95% CI: 0.64, 1.02). There was a considerable heterogeneity across studies ($I^2 = 88.2\%$, P-heterogeneity < 0.001) (**Supplemental Figure 15**, Table 1). The finding was the same after considering adjusted effect sizes for intermediate variables (RR: 0.83; 95% CI: 0.68, 1.01, $I^2 = 83.2\%$; **Supplemental Figure 16**). Stepwise exclusion of each study in the sensitivity analysis revealed that the results of the "Linxian Nutrition Intervention Trials" study influenced the association (51). Excluding this study from the main analysis resulted in a significant inverse association between egg intake and risk of stroke mortality (RR: 0.76; 95% CI: 0.61, 0.95; **Supplemental Figure 17**). Based on subgroup analyses, geographical location, case number, and adjustments for energy intake, physical activity, and alcohol consumption, and controlling for hypertension, blood pressure, diabetes, and serum cholesterol were potential sources of between-study heterogeneity (**Supplemental Table 14**). The summary RR for men was 0.32 (0.14, 0.73; $n = 2$) and 1.32 (0.52, 3.30; $n = 2$) for women. Furthermore, there was a significant inverse association between exposure and the outcome among studies with a less than 15-y follow-up period (RR: 0.74; 95% CI: 0.56, 0.98; $n = 6$), populations with a mean egg intake of 3 or more eggs/wk (RR: 0.72; 95% CI: 0.56, 0.92; $n = 6$), and studies with a high number of deaths ($\geq$500; RR: 0.71; 95% CI: 0.51, 0.98; $n = 3$). This inverse relation was also found in studies that controlled the analysis for alcohol consumption, hypertension, and diabetes.

The linear trend estimation based on all studies revealed that an additional intake of 1 egg/wk was associated with a 4% lower risk of stroke mortality (RR: 0.96; 95% CI: 0.92, 0.99; **Supplemental Figure 18**). However, there was no nonlinear association (P-nonlinearity $= 0.84$; Figure 2 and Supplemental Table 9). The funnel plot (Supplemental Figure 26D) and Egger's test ($P = 0.30$) revealed no evidence of publication bias. The quality of evidence was moderate (Supplemental Table 11).

Egg and cancer mortality

Thirteen prospective cohorts (10, 18, 40, 43–45, 47, 51, 53, 55, 57–59), with a total of 895,308 participants and 60,799 deaths, were included in this analysis; based on these, we found that egg consumption was associated with a 20% higher risk of cancer mortality (RR: 1.20; 95% CI: 1.04, 1.39), again with a considerable heterogeneity across studies ($I^2 = 93.6\%$, P-heterogeneity < 0.001) (**Supplemental Figure 19**, Table 1). Excluding each study once at a time did not impact the association (**Supplemental Figure 20**). We found a similar positive association in a further analysis in which the effect of intermediate variables was taken into account (RR: 1.11; 95% CI: 1.0, 1.22; $I^2 = 80.8\%$, **Supplemental Figure 21**). Based on subgroup analyses, gender could explain between-study heterogeneity (**Supplemental Table 15**). The summary RR for men was 1.40 (1.10, 1.76; $n = 5$) and 1.49 (1.04, 2.1; $n = 5$) for women. The positive significant association was observed in studies conducted in the United States (RR: 1.33; 95% CI: 1.11, 1.60; $n = 4$), those that included only men (RR: 1.72; 95% CI: 1.20, 2.47; $n = 2$), cohorts with a follow-up period of more than 15 years (RR: 1.24; 95% CI: 1.02, 1.51; $n = 6$), and studies with fewer than 500 deaths (RR: 1.45; 95% CI: 1.15, 1.85; $n = 8$).

All studies, except for Khan et al. (43), had reported sufficient data for inclusion in the dose-response analysis. According to the linear dose-response meta-analysis, eating 1 more egg per week was associated with a 4% increased risk of cancer mortality (RR: 1.04; 95% CI: 1.01, 1.07; **Supplemental Figure 22**). The dose-response analysis also revealed a direct relation between egg consumption and cancer mortality risk (P-nonlinearity $= 0.47$, P-linearity $= 0.002$; Figure 2 and Supplemental Table 9). No evidence of publication bias was detected by funnel plot (Supplemental Figure 26E) and Egger's test ($P = 0.63$). The evidence was judged to be of moderate quality, with downgrades for inconsistency and indirectness, and an upgrade for dose-response gradients (Supplemental Table 11).

Egg and respiratory disease mortality

The analysis of egg consumption with risk of respiratory disease mortality, based on 3 cohort studies with 149,474 participants and 2161 deaths (10, 55, 57), revealed no significant association (pooled RR: 0.96; 95% CI: 0.53, 1.71). There was a high degree of heterogeneity ($I^2 = 88.4\%$, P-heterogeneity < 0.001) (**Supplemental Figure 23**, Table 1). The observed null association did not change by including adjusted effect sizes for potential intermediate risk factors (RR: 1.05; 95% CI: 0.62, 1.78; $I^2 = 82.9\%$; **Supplemental Figure 24**). Excluding the study of Chen et al. (57) from the main analysis revealed a significant inverse association between egg intake and respiratory disease mortality (RR: 0.73; 95% CI: 0.54, 0.97; **Supplemental Figure 25**). All studies were included in the dose-response analysis. The summary RR for increasing 1 egg per week was 0.99 (95% CI: 0.0.91, 1.08; **Supplemental Figure 26**). In addition, there was no evidence of a nonlinear association (P-nonlinearity $= 0.46$; Figure 2 and Supplemental Table 9). The certainty of evidence was moderate (Supplemental Table 11).

Discussion

Principal findings

This meta-analysis summarized epidemiologic evidence from 33 prospective cohort studies by comparing extreme categories and performing dose-response analyses for both linear and nonlinear relations. No evidence of an association between egg consumption and risk of mortality from all causes and CVD, stroke, CHD, and respiratory disease was seen; however, there was a significant positive association between egg consumption and risk of cancer mortality. In the linear dose-response meta-analysis, we observed 4% and 2% greater risks of mortality from cancer and all causes, respectively, and a 4% lower risk of mortality from stroke by an additional 1-egg intake per week.

Comparison with other studies

Egg has long been debated as one of the main drivers of dietary cholesterol intake. We found a null association between the highest compared with the lowest intake of egg and risk of total mortality, but an increased risk was observed for each additional egg consumed per week. As a result, low egg consumption could not have a negative impact on mortality and supports the latest American Heart Association Dietary Guidelines (60). Our finding was in line with 2 earlier studies that found no association between egg consumption and risk of all-cause mortality (24, 61). In contrast, Schwingshackl et al. (15) found an increased risk of 10% for total mortality by egg intake up to 60 g/d. However, there was a significant between-study heterogeneity and a low quality of evidence in that finding. Similarly, in a pooled analysis of 6 US-based cohorts, each additional 300-mg/d dietary cholesterol intake was associated with a significant greater risk of all-cause mortality (62). Different participant characteristics and high doses of dietary cholesterol intake, which were much higher than the global average of 228 mg/d (63), might provide some reasons for such a discrepant finding.

We failed to find any significant association between egg consumption and risk of CVD mortality. This was consistent with earlier findings of meta-analyses (24, 64–66). In a recent dose-response meta-analysis of prospective cohort studies, Godos et al. found no significant association between habitual consumption of 1 egg/d, compared with no consumption, and risk of cardiovascular outcomes (67). Opposite to ours, an old meta-analysis in 2013 reported a 19% increased risk of CVD comparing extreme categories of egg intake (68). Inconsistencies between our results and the aforementioned study could be due to the fact that, later in that study, more prospective literature with different findings was generated, which provided the necessary opportunity to do a more complete and more in-depth analysis of evidence. Comparing our findings with the pooled analysis of 6 US-based cohorts, again there was a controversy. Zhong et al. (62) reported a direct association between dietary intakes of egg and cholesterol and risk of incident CVD. It must be kept in mind that, in Western countries, egg consumption was frequently associated with an unhealthy lifestyle, such as smoking, lack of physical activity, and poor dietary habits (69), that might confound the associations with CVD.

With regard to CHD mortality, we failed to find a link with egg consumption. This was in agreement with the vast majority of earlier meta-analyses (61, 64, 70, 71). In a recent dose-response meta-analysis of 16 prospective studies about egg consumption and risk of CHD incidence/mortality, the investigators found no significant relation for consuming more than 2 eggs/wk (67). Previous pooled and meta-analyses on the association of egg consumption with stroke incidence/mortality found either null associations (64, 65, 67, 71, 72) or significant inverse associations (61, 24, 70). The observed beneficial effect on cardiovascular health in earlier studies might be supported by other prophylactic components of eggs. Egg phospholipids can raise HDL-cholesterol concentrations and improve HDL function by preferentially incorporating into HDL-cholesterol particles (73), thereby attenuating the progress of atherosclerosis (74). Furthermore, high-quality egg proteins have been shown to increase satiety and lower postprandial glycemia and insulinemia in both healthy and overweight people (75, 76). Higher bioavailability of egg-derived carotenoids (lutein, zeaxanthin) and their role in improving the absorption of carotenoids from fruits or vegetables (77) might result in antioxidant and anti-inflammatory effects against atherosclerosis (78).

We observed a positive association between egg intake and risk of cancer mortality. This was consistent with previous studies on risk of several cancers. In a dose-response meta-analysis of prospective observational studies, consumption of more than 5 eggs/wk was associated with a modestly elevated risk of breast, ovarian, and fatal prostate cancers (79). The Health Professionals Follow-Up Study, which followed over 27,000 men for 14 y, found that men who consume 2.5 eggs/wk were 1.8 times more likely than men who consume 0.5 eggs/wk to develop lethal prostate cancer (47). It has been proposed that the choline content of eggs may contribute to an increased risk of lethal prostate cancer (80). Despite a large body of evidence supporting an association between egg consumption and cancer risk or mortality, there was considerable inconsistency, such that several studies failed to observe a significant association (55, 57, 81). These discrepancies between studies may be explained by the high degree of heterogeneity associated with different analytic comparisons, cooking methods, differences in consumption, study locations, follow-up duration, and adjusted for different covariates. For instance, the positive association was only significant in cohort studies conducted in the United States, but not in Asian or European studies. In addition, a meta-analysis of 184,727 participants found no association between total egg consumption and bladder cancer incidence, but fried eggs were positively associated with bladder cancer risk due to the formation of heterocyclic amines during high-temperature frying (81). In light of this, further high-quality studies incorporating these variables would be critical to understanding this association.

We found no association between higher egg intake and mortality from respiratory diseases. A small body of prospective studies were available testing this relation (82, 55). In a cohort study, no significant association was observed between dietary cholesterol intake and mortality from respiratory disease when extreme categories were compared; on the contrary, consuming more than 1 egg/d in that study was associated with a greater risk (83). It must be kept in mind that participants in that study were postmenopausal women aged 50–79 y.

Taken together, previous meta-analyses found that higher consumption of whole grains, nuts, fruits, and vegetables was associated with an 18%, 19%, 9%, and 7% reduced risk of total mortality, respectively, while higher consumption of red meat, processed meats, and sugar-sweetened beverages was associated with a 10%, 21%, and 8% increased risk, respectively (15, 84–86). We found a 2% increase in the risk of total mortality for each additional egg consumed per week. This may imply that egg consumption has a less significant effect on mortality outcomes than other food groups.

Mechanisms

Several mechanisms could account for the observed neutral association between egg consumption and mortality from all-cause, CVD, CHD, stroke, and respiratory disease. Elevated serum total cholesterol and LDL-cholesterol concentrations are major triggers in the development of CVD and its associated risk factors. Epidemiologic evidence suggests a modest increase in serum LDL- and HDL-cholesterol concentrations with no effect on the ratio of LDL to HDL cholesterol among hyperresponders (individual responses to dietary cholesterol as hyperresponders or hyporesponders), following egg-derived dietary cholesterol intake (87–89). It is noteworthy that each additional 100-mg intake of dietary cholesterol consumed increased LDL-cholesterol concentrations by 1.9 mg/dL and HDL-cholesterol concentrations by 0.4 mg/dL (90). Given that the consumption of eggs was associated with an increase in LDL-cholesterol peak diameter and a decrease in smaller LDL-cholesterol subfraction, a less atherogenic lipoprotein profile would be appear (91, 92). Furthermore, beneficial effects of other components in egg, such as high-quality protein, vitamins of the B-complex, folate, fat-soluble vitamins, and several essential minerals, cannot be ruled out. Egg-derived phospholipid raises HDL cholesterol, which may counteract the adverse effect of egg on LDL cholesterol (73). It has been shown that vitamin B supplementation might decrease the risk of stroke (93). A multiracial prospective cohort study found an inverse relation between serum 25-hydroxyvitamin D concentrations and mortality (94). The plausible mechanisms behind a direct association of egg intake with mortality from cancer may be as follows: egg yolk has been suggested to increase the frequency of gallbladder contraction, resulting in increased bile acid secretion to the intestine (95). Of note, the carcinogenic property of bile acids for gastrointestinal cancer was shown before (96). Eggs are particularly high in choline, which is essential for cell functions involved in cancer growth and progression (97). Disruption in cholesterol homeostasis, combined with aging and malignant cells, results in cholesterol accumulation, which may act as a precursor for androgen production and alter signaling pathways to promote cancer progression (98, 99).

Strengths and limitations

The primary strength of the current meta-analysis is that it includes studies with a prospective cohort design that reduces the impact of reverse causation and selection bias, which are common in cross-sectional or case-control studies. Our analyses included a large number of participants and deaths, which increased statistical power and allowed us to quantify the association between egg consumption and mortality. In addition, we conducted linear and nonlinear dose-response analyses, which provided compelling evidence for the quantitative examination of relations in order to clarify the strength and shape of the observed associations. Other strengths include using broad search terms; performing extensive subgroup, sensitivity, and influence analyses; and evaluating the risk of bias as well as the certainty of evidence for each association. Finally, we separately examined the associations for a group of cause-specific mortality.

Several limitations should also be considered when interpreting our findings. First, we observed considerable evidence of heterogeneity between studies, which could be explained by the variation in study location, follow-up duration, gender, dietary assessment methods, number of participants, and covariate adjustment. Second, measurement errors in egg intake and other dietary habits could have diluted individual study results that can, in turn, result in a null association. The majority of included studies measured egg consumption in a single assessment at study baseline, and changes in egg consumption over time were not taken into account. Third, most existing studies lacked information on the method of cooking eggs and the amount of added salt. The nutritional value of eggs can vary depending on how they are cooked (9). Fourth, the magnitude of the association could have been influenced by residual or unmeasured confounders. While the majority of studies accounted for potential confounders, some did not consider additional dietary factors and nutrients. The lack of controlling for these factors, such as the amount of protein and cholesterol in the diet, of which eggs are the main source, may have an effect on the observed association. Fifth, the association between dietary egg consumption and risk of CVD, stroke, and respiratory disease mortality was not robust in the influence analysis and was based on a single study. Therefore, additional research is required before conclusive evidence can be formed on the association between egg consumption and these outcomes. Sixth, skipping breakfast has not been considered in the included studies as a potential confounder due to the fact that eggs are usually consumed at breakfast along with other foods such as milk, cheese, bread, and tea, which can vary by country. It is suggested that future studies consider breakfast skipping as well as breakfast foods as a potential confounder. Finally, 1 major limitation of any meta-analysis is that it cannot address the issue of substitution, which is crucial in practice. These findings are likely to vary depending on the comparison; for example, eggs are good when compared with a (very common) starch and refined-sugar breakfast, but they may not be as good as a breakfast with whole grains, nuts, and dates.

Conclusions, policy implications, and future research

In conclusion, our findings did not support the hypothesis that higher egg consumption is related to increased risk of mortality from most causes; however, egg consumption was associated with an elevated risk of cancer mortality. Our findings suggest that the recommendation of habitual egg consumption as part of a healthy diet, as recommended in the *2020–2025 Dietary Guidelines for Americans* (100), should be done with caution, and additional research, particularly among patients with cancer, heart disease, and diabetes, is necessary to better understand the observed associations. Further prospective studies in low-income and African countries, where eggs may be the main dietary source to meet protein requirements, are recommended. In addition, future studies should consider cooking methods of eggs in their contribution to several health-related outcomes. Substituting other protein sources and food groups for eggs also needs further investigation.

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